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4.(currently amended) An isolated nucleic acid molecule comprising at least [[24]] 80 contiguous bases of nucleotide sequence first disclosed in SEQ ID NO: 3.

Please add new claims 5 and 6 to read as follows

C1

5.(new) An expression vector comprising a nucleic acid molecule of Claim 1.

6.(new) A cell comprising the expression vector of Claim 5.

RESPONSE

I. Status of the Claims

Claims 2, 3 and 4 have been amended. Claims 5 and 6 have been added. Claims 1-6 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**. A marked up copy of the original title is attached hereto as **Exhibit B** and clean copy of the amended title is hereto as **Exhibit C.**

II. Support for the Amended Specification and Claims

Claim 2 has been amended to further clarify the claim, and to recite that the stringent hybridization conditions are those used as an example in the specification as filed. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in Claim 2 as originally filed and on page 4, lines 20-25.

Claim 3 has been amended. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in Claim 3 and the sequence listing as originally filed and on page 5, line 19.

Claim 4 has been amended. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in Claim 4 and the sequence listing as

originally filed and on page 5, line 19.

Claim 5 has been added to better claim the present invention. New Claim 5 is supported by the specification as originally filed with particular support being found on or about page 13, lines 22-28.

Claim 6 has been added to better claim the present invention. New Claim 6 is supported by the specification as originally filed with particular support being found on or about page 13, line 28 through page 14, line 1.

As the amendments to claims 2-4 and new claims 5 and 6 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry therefore is respectfully requested.

III. Objection

The Action objects to the title of the disclosure because it recites the term "novel" and allegedly because all patents contain novel subject matter this term should be removed. Applicants in no way agree. However, in order to progress the application more rapidly towards allowance, Applicants have amended the title of the present application to read: POLYNUCLEOTIDES AND POLYPEPTIDES ENCODING HUMAN GABA RECEPTORS PROTEINS. In amending the title, Applicants have carefully considered the Examiner's remarks. However, as the present application discloses polypeptide sequences and both claims 1 and 2 refer to amino acid sequences, Applicants have chosen in the interest of accuracy and completeness to include the term "polypeptide" in both the title and abstract.

IV. Rejection of Claims 1-4 Under 35 U.S.C. § 101

The Action first rejects claims 1-4 under 35 U.S.C. § 101 because the claimed invention is not supported by a specific and substantial asserted utility, or a well established utility.

The Action states that the "instant application does not disclose a specific and substantial biological role" for the claimed sequences or "their significance" Therefore no specific and substantial utility can be asserted (Action at page 3, lines 7-10). Applicants respectfully disagree, as Applicants have clearly asserted that the presently claimed sequences as encoding novel human GABA receptors.

This assertion is stated in the title of the application, "Novel Human GABA Receptors and Polynucleotides encoding the same" in the title. The novel human proteins encoded by the sequences of the present invention are said to be similar to human and other mammalian GABA receptors (on page 2, lines 4-5) and are said to "share structural similarity with GABA receptor proteins, and particularly GABA A receptor gamma-1, -2, and -3, -4, -5, and -6 subunits" (page 16, lines 7-9). In addition, the assertion is also made when the specification discloses the well recognized biological roles of GABA receptors, which are well known to the art (Section 2). As GABA receptors their biological role is well known to those of skill in the art, as stated in the specification "Because of their medical relevance, GABA receptors have been subject to considerable scientific scrutiny as shown in U.S. Application No. 09/183,253 (corresponding to WO9942580A2), herein incorporated by reference, which describes a variety of uses, assays, and applications" (page 16, lines 9-13). Additionally, biologic roles were described in the Section 2 of the specification "GABA receptors bind potent inhibitory neurotransmitters and this interaction serves as a target for a variety of pharmaceutically active agents such as benzodiazepines, barbiturates, and alcohol" (Page 1, lines 26 -28). Thus clearly Applicants have asserted the sequences of the present invention encode human GABA receptors and that the biologic role of GABA receptors is well known to the art.

As a further example of how well accepted the role of GABA receptors is, Applicants quote the introduction of Chapter 16 of the sixth edition of the textbook Basic Neurochemisty:Molecular, Cellular and Medical Aspects, Editied by George J. Siegal, *et al.* (Lippincott, Williams & Wilkens).

> *"γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). It was discovered in 1950 by Roberts and Awapara. Electrophysiological studies between 1950 and 1965 suggested a role for GABA as a neurotransmitter in the mammalian CNS. Since then, GABA has met the five classical criteria for assignment as a neurotransmitter: it is present in the nerve terminal, it is released from electrically stimulated neurons, there is a mechanism for terminating the action of the released neurotransmitter, its application to target neurons mimics the action of inhibitory nerve stimulation and specific receptors exist.*

In view of the ubiquitous nature of GABA in the CNS, it is perhaps not too surprising that its functional significance should be far-reaching. A growing body of evidence suggests a role for altered GABAergic function in neurological and psychiatric disorders of humans, including Huntington's disease, epilepsy, tardive dyskinesia, alcoholism, schizophrenia, sleep disorders, Parkinson's disease and mental retardation. Pharmacological manipulation of GABAergic transmission is an effective approach for the treatment of anxiety [1]. In addition, it has been demonstrated that the nervous system-depressant actions of barbiturates and other general anesthetics result from an enhancement of inhibitory synaptic transmission mediated by $GABA_A$ receptors [2,3]."

Textbooks are, by their very nature, representative of concepts generally accepted by those of skill in the art and thus clearly the utility of a novel human GABA receptors would be readily recognized by those of skill in the art, as among others, valuable drug targets for neurological disease.

The Action incorrectly states that "it is clear from the instant specification that the claimed receptor is what is termed an "orphan receptor" (page 3, lines 11-12). Applicants have identified the sequences of the present invention as encoding novel human GABA receptors. The Action's assumption appears to be based in part of the finding that the sequences of the present invention share limited similarity to rat GABA(A)receptor gamma-1 subunit mRNA. This discrepancy probably results because, as Applicants have asserted, the sequences of the present invention encode human GABA receptor. Evidence of the credibility of Applicants' assertion that the sequences of the present invention encode human GABA receptors is the fact that SEQ ID NO:2 shares greater than 99% identity with a protein present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists *wholly unaffiliated with Applicants* as "Gamma-aminobutyruc-acid receptor gamma-1 subunit precursor (GABA(A) (accession number Q8N1C3; alignment and GenBank report provided in **Exhibit D**). Thus, clearly, when those of skill in the art were faced with identifying the product of the sequences of the present invention, they readily recognized and concurred with Applicants assertion that they encode human GABA receptors. Therefore, clearly Applicants assertion regarding the identity and utility of the sequences of the present invention are credible to those of skill in the art.

Further evidence supporting Applicants' position regarding the biological function of the protein encoded by the sequences of the present invention is the result obtained using the Conserved Domain Architecture Retrieval Tool (CDART; **Exhibit E**). A CDART analysis of the present protein sequences demonstrates that these sequences encode a neurotransmitter-gated ion-channel binding domain and a neurotransmitter-gated ion-channel transmembrane region. As GABA is a well known and long established neurotransmitter, clearly this finding is consistent with Applicants' assertion that these sequences encode human GABA receptors.

While the sequences of the present invention have been clearly shown to encode GABA receptors, it is the Actions position that knowing a proteins structure is insufficient to identifying its funtion. Applicants disagree and strongly believe that the vast majority of those of skill accept the concept that there is a structure function relationship. In support of its position the Action cites an article by Skolnick, *et al.* (Trends in Biotech *18*:34-39, 2000) for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (Skolnick at page 36, emphasis added). However, Skolnick, *et al.* concerns predicting protein function not by overall amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting that such methods have correctly assigned function in 50-70% of the cases, thus a majority of the time supporting rather than refuting Applicants assertions.

The Action next cites Bork (Genome Research *10*:398-400, 2000) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The Action directs attention to page 399, on which the author notes the limitations of various methods of analysis. It is of interest that in his "analysis" Bork often uses citations to many of his own previous publications, an interesting approach. ' My position is supported by my previous disclosures of my position.' If Bork's position is supported by others of skill in the art, one would expect that he would reference them rather than himself to provide support for his statements. Given that the standard with

regard to obtaining U.S. patents is those of skill in the art, this observation casts doubt on the broad applicability of Bork's position. It should also be noted that in Table 1,on page 399, in which selected examples of prediction accuracy are presented, that the reported accuracy of the methods which Applicants have employed are, in fact, very high. While nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, " Homology (several methods)" is assigned an accuracy rate of 98% and "Functional features by homology" is assigned an accuracy rate of 90%. Given that these figures were obtained based on what is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Applicants assertions in the present case. Additionally Bork even states (on page 400, second column, line 17) that " However, there is still no doubt that sequence analysis is extremely powerful". In summary, it is clear that it is not Bork's intention to refute the value of sequence analysis but rather he is indicating that there is room for improvement .

The action next cites Doerks *et al.* (Trends in Genetics *14*:248-250, 1998) in support that sequence-to-function methods of assigning protein function are prone to errors due to partial annotation, multifunctionality and over prediction. However, Doerks *et al.* states that "utilization of family information and thus a more detailed characterization" should lead to "simplification of update procedures for the entire families if functional information becomes available for at least one member" (Doerks *et al.*, page 248, paragraph bridging columns 1 and 2, emphasis added). Applicants point out that transporters represent a well-studied protein family with a large amount of known functional information, exactly the situation that Doerks *et al.* suggests will "simplify" and "avoid the pitfalls" of previous sequence-to-function methods of assigning protein function (Doerks *et al.*, page 248, columns 1 and 2). Thus, instead of supporting the Action's position against utility, Doerks *et al.* supports Applicants' position that the presently claimed sequences have a recognized substantial and credible utility.

The Examiner also cites Smith, *et al.* (Nature Biotechnology *15*:1222-1223, 1997) as teaching "that there are numerous cases in which proteins of very different functions are homologous" (Action at page 4). However, the Smith, *et al.* article also states "the major problems associated with nearly all of the current automated annotation approaches are - paradoxically - minor database annotation inconsistencies (and a few outright errors)" (page 1222, second column, first paragraph, emphasis

added). Thus, Smith, *et al.* do not in fact seem to stand for the proposition that prediction of function based on homology is fraught with uncertainty, and thus also does not support the alleged lack of utility.

The Examiner next cites Brenner (Trends in Genetics *15*:132-133, 1999) as teaching that proposition that accurate inference of function from homology is a difficult problem . However, this statement is based on the assumption that "if there are only 1000 superfamilies in nature, then most homologs must have different molecular and cellular functions" (page 132, second column). Furthermore, Brenner suggests that one of the main problems in using homology to predict function is "an issue solvable by appropriate use of modern and accurate sequence comparison procedures" (page 132, second column), and in fact references an article by Altschul *et al.*, which is the basis for one of the "modern and accurate sequence comparison procedures" used by Applicants. Thus, the Brenner article also does not support the alleged lack of utility.

Finally, the Action finally cites Bork *et al.* (Trends in Genetics *12*:425-427, 1996) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The question as to whether Bork's positions are generally supported by those of skill in the art was discussed above in the paragraph regarding the other Bork citation. It should also be noted that this article was published approximately 6 years ago and thus refers to errors or "traps" associated with earlier algorithms and technologies in a field that has undergone constant improvement. This publication identifies (Table 1) various areas in which incorrect information appears in sequence databases. These "traps" include Synonyms - a single gene having a variety of names, Different gene-same name- when the same name is used to describe different genes, Spelling errors, Contamination- the unintentional inclusion of vector sequences, etc. and propagation of incorrect functional associations based on poorly analyzed homology. All of these issues can effect the accuracy of sequence base analysis, however all can be overcome by a more careful analysis as would be done by one of skill in the art. Automatic methods of sequence homology as identified by any algorithm is a staring point for consideration, and one of skill in the art can then through further analysis, structure-function analysis, etc. can and should then verify the associations. For example in addition to algorithm based sequence analysis the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1 B.S. and 4 Ph.D. level scientists). Clearly such highly skilled and careful analysis reduces the influence of such "traps". Furthermore, in the final section of this

publication (page 427) it again becomes cleat that Bork *et al.* do not discount the value of sequence analysis "we wish to point out that sequence database are the most useful tool in sequence analysis and the question should be how can one further improve their value". Thus clearly this publication represents a call to action to enhance the already high value of sequence analysis rather than an indictment of the utility of sequence based analysis. Therefore, as Bork *et al.* identifies the high value of sequence based analysis it actually supports rather than refutes Applicants assertions regarding the utility of the present invention.

In summary a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1 B.S. and 4 Ph.D. level scientists). These articles are merely examples of a small number of spurious publications that call into doubt the usefulness of bioinformatic predictions and that the PTO has repeatedly attempted to use as a basis to deny the utility of nucleic acid sequences. However, without going into the merits (or lack thereof) of all of the cited articles, Applicants point out that the lack of 100% unanimous agreement on the usefulness of bioinformatic prediction programs or the derivation of function using established domains and motifs is completely irrelevant to the question of whether the claimed nucleic acid sequence has a substantial and specific utility. Applicants respectfully point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be **believable**. Applicants submit that the overwhelming majority of those of skill in the relevant art **believe** bioinformatic prediction to be a powerful and useful tool, and that the derivation of function using established protein domains and shared motifs is often essential to defining function, this is evidenced by hundreds if not thousands of journal articles

Applicants submit that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable.

As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well

> before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. The Examiner states that a "real-world" utility "does not require further research" (Action at page 4). However, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of <u>further research and development</u>" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin*, *supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, *supra*.

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered <u>credible</u> by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001). Given this clear and convincing evidence that those of skill in the art would and have recognized the sequences of the present invention as encoding human GABA receptors, whose function is very well-established. Thus clearly, there can be no question that Applicants' asserted utility for the described sequences is "<u>credible</u>." Applicants have thus supplied evidence supporting their assertion that those of skill in the art would recognize that the sequences of the present invention encode GABA receptors, and therefore

have all the well recognized utility thereof. As such, the scientific evidence clearly establishes that Applicants have described an invention whose utility is in full compliance with the provisions of 35 U.S.C. § 101, and the Examiner's rejection should be withdrawn.

Furthermore, it should be noted that the present situation directly tracks Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when a full length sequence (such as the presently claimed sequence), and has a similarity score greater than 95% to a protein having a known function (such as the greater than 99% identity between the presently claimed sequence and the cited GABA receptor of Q8N1C3). Thus, the present utility rejection must fail as a matter of policy and a matter of law.

Additionally, the Action, (page 3, lines 1) identifies the instant situation as "directly analogous to that addressed in Brenner v. Mason, 148 U.S.P.Q. 689 (Sus. Ct., 1966) in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent". Applicants respectfully disagree with the Action's assertion that this is a direct analogy. An activity, such as anticancer activity, is clearly distinct from a term that defines a molecules function. In the present invention, the term GABA receptor clearly defines a membrane protein as a receptor for the neurotransmitter GABA. In contrast a term of activity, such as anticancer activity, may or may not identify a specific function. There are many ways in which a compound can have anticancer activity, it can have one or more specific functions, such as but not limited to the ability to inhibit enzymes involved in DNA synthesis or repair. Thus, it is Applicants position that those of skill in the art would readily recognize that the term activity can be used in a broader sense and that such was the case with the term anticancer activity as used in *Brenner v. Manson.*

As still another example of utility of the present nucleotide sequences, Applicants point out that, as taught in the specification as originally filed the claimed polynucleotide sequences can be used to track the expression of the genes encoding the described proteins. In particular, the specification describes how the described sequences can be represented using a gene chip format to provide a high throughput analysis of the level of gene expression. Such "DNA chips" clearly have utility, as evidenced

by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. Evidence of the "real world" substantial utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Agilent Technologies, Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value (net equity value of the transáction was $620 million) that it was acquired by large pharmaceutical company, Merck & Co., for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. The sequences of the present invention describe a novel gene encoding a GPCR and provide a unique identifier of the corresponding gene. Such gene chips clearly have utility, as evidenced by hundreds of issued U.S. Patents, such as U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. The present nucleotide sequences clearly encode human GPCRs, as detailed throughout the specification. The specification also teaches that GPCRs are associated with a wide variety of cellular functions, and as such, that GPCR interacting proteins have been subject to intense scrutiny as potential drug targets. Therefore, as the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such gene chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

An additional utility of the present invention is in expanding the utility of data coming from the human genome project. Persons of skill in the art, as well as thousands of venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. All current therapeutics used in humans directly or indirectly interact with biological sequences encoded by the human genome, and virtually all future human therapeutics shall do likewise. Consequently, billions of dollars have been invested in the human genome project,

resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success, as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotide, the present nucleotide sequence has a specific utility in mapping the protein encoding regions of the corresponding human chromosome, as detailed in the specification Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, s Only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Board is requested to review, for example, section 3 of Venter *et al.*

(*supra at* pp. 1317-1321, including Fig. 11 at pp. 1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As evidence of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit F**. This is the result of a blast analysis using SEQ ID NO:1 of the present invention when overlaid upon the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 11 different exons spread non-contiguously along a region of human chromosome 4 (4p12), which is represented by clones AC0095058 and AC096592. Thus clearly one would not simply be able to identify the protein encoding exons that make up the sequence of the present intention, nor to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what the specific sequences were. Additionally, it should be noted that the gene of Q8N1C3 (**Exhibit D**), Gamma-aminobutyric-acid receptor gamma-1 subunit precursor (GABA(A) receptor also maps to the same region of human chromosome 4. Thus further supporting Applicant's assertion that the sequences of the present invention encode a variant of the human GABA(A) receptor.

Finally, with regards to the issue of due process, while Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S.

Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants agree that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Given the rapid pace of development in the biotechnology arts, it is difficult for the Applicants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Applicants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

Thus in summary, Applicants submit that the presently claimed molecules have been shown to encode, as asserted in the specification as filed, GABA receptors, whose biological function is very well-established. Thus, the present situation directly tracks Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when a full length sequence (such as the presently claimed sequence), and has a similarity score greater than 95% to a protein having a known function (such as the greater than 99% identity between the presently claimed sequences and those of the cited GABA receptor of Q8N1C3). Furthermore this response has described a series of additional substantial, specific, credible and well-established utilities for the present invention. Therefore, Applicants submit that as the presently claimed sequence molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of the claims under 35 U.S.C. § 101 has been overcome. Thus, Applicants respectfully request that the rejection

be withdrawn.

V. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse. Applicants submit that the GABA receptor encoding sequences of the present invention have been shown to have "a specific, substantial, and credible utility", as detailed in the section above. Applicants therefore request that the rejection of the claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Action also rejects claims 3 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which is not described in the specification ins such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants in no way agree with the Examiner's position that original Claims 3 and 4 lack enablement. The relevant question is would the skilled artisan know how to make and/or use the claimed nucleic acid sequence? The answer is clearly yes, the skilled artisan would easily recognize 80 contiguous nucleic acids derived from any of the nucleic acid sequences described in the sequence listing and know how to make an isolated nucleic acid comprising 80 contiguous nucleic acids of SEQ ID NO:1 or 3. Those of skill in the art would also know how to use a nucleic acid molecule that comprises 80 contiguous bases of nucleic acid sequence of SEQ ID NO: 1 or 3. In fact, Applicants note that the entire DNA gene chip industry is based on the use of 80 or more contiguous bases of nucleic acid sequence. Therefore, Applicants submit that those of skill in the art would also be able to make and use the present invention. Thus, one skilled in the art would know how to make and/or use the nucleic acid sequence of original Claims 3 and 4 and the present invention is thus enabled. Therefore, Applicants respectfully request that the rejection of Claims 3 and 4 under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Action also rejects claims 1 and 3 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession

of the claimed invention. Allegedly because Claims 1 and 3 encompasses the phrase "at least 24 continuous bases". Applicants note that Claim 1 does not contain this phrase, however Claim 4 does, therefore Applicants will assume that this rejection is in fact directed at claims 3 and 4, not claims 1 and 3 as stated in the Action.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.*" *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the ... nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity

> what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides comprising the nucleotide sequence of at least 80 contiguous bases of, for example, SEQ ID NO:1 or 3, are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. In other words those that do not contain at least 80 contiguous bases of these sequences lie outside the genus. Thus those of skill in the art would have known how to make and use the invention as claimed in original Claim 3

and 4.

Furthermore Applicants respectfully submit that recently issued US Patents have contained this same phrase (See for example 6,403,784 and 6,583,269),thus the office has a history of recognizing the patentability of such claims. Since claims within issued US patents are presumed to meet the requirements for utility, enablement and written description and for the additional reasons stated above, Applicants submit that the present invention meets both the requirements for enablement and written description and respectfully request that the rejection of Claims 3 and 4 under 35 U.S.C. § 112, first paragraph, be withdrawn.

VI. Rejection of Claim 2 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects claim 2 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Action rejects Claim 2 as allegedly indefinite based on the term "stringent" in regards to hybridization conditions. While Applicants submit that the term is sufficiently definite, as a number of stringent hybridization conditions are defined in the specification and would be known to those of skill in the art, solely in order to progress the case more rapidly toward allowance the claim has been revised to recite the exact hybridization conditions described as an example in the specification as originally filed (page 4, lines 20-25). Applicants submit that revised Claim 2 now even more clearly meets the requirements of 35 U.S.C. § 112, second paragraph. Applicants stress that "a claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). Based on the foregoing, Applicants submit that Claim 2 is sufficiently definite, and respectfully request withdrawal of this rejection.

VII. Rejection of Claims 3 and 4 Under 35 U.S.C. § 102

The Action next rejects claims 3 and 4 under 35 U.S.C. § 102(b), as being anticipated by Ymer *et al.* (Accession No. X57514).

While Applicants do not necessarily agree with the present rejection, as Claims 3 and 4 have

been amended to recite at least 80 contiguous bases of the nucleotide sequence of SEQ ID NO:1 or 3, which is neither taught nor suggested by Ymer *et al.* (Accession No. X57514) Applicants therefore submit that the rejection of claims 3 and 4 under 35 U.S.C. § 102(b) has been thus avoided, and respectfully request withdrawal of the rejection.

VIII. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Landsman have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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